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Claims 1-4 are currently pending in the present application. Applicants acknowledge the Examiner's acceptance of the election of the claims 1-4 to prosecute in the present application.

In the Office Action dated May 12, 2003, the Examiner objected to the specification of certain grounds and rejected claims 1-4 on other grounds. Applicants will address and traverse each of the Examiner's grounds for objection and rejection in this Reply, thereby placing the present application in condition for allowance.

I. Priority

In numbered paragraph 5 of the Office Action, the Examiner indicated that priority to the earlier filed application U.S. Serial No. 08/741,866 would not be granted because the claimed subject matter of the present invention is not disclosed in that application. Applicants submit that this action of the Examiner is improper and Applicants should be granted priority based on the earlier application.

The present application is a continuation of U.S. Serial No. 09/220,363 filed December 24, 1998, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/741,866 filed September 26, 1996, which is now U.S. Patent No. 5,854,992. This information about the present application is confirmed by the Official Filing Receipt attached as Attachment 1 to this Reply.

The specification of the present invention is the same as the specification of U.S. Serial No. 09/220,363. This specification supports pending claims 1-4 of the present invention. This specification of U.S. Serial No. 09/220,363 and the present application contain additional subject matter compared to U.S. Serial No. 08/741,866, thus U.S. Serial No. 09/220,363 was filed as a continuation-in-part application. Since the present application is a continuation of U.S. Serial No. 09/220,363 not 08/741,866, the Examiner should grant priority as specified in the Official Filing Receipt and withdraw this rejection.

II. Specification

In numbered paragraph 6 of the Office Action, the Examiner objected to the title as being non-descriptive on the claimed invention. Applicants have reviewed the pending claims on the application and have amended the title as appropriate to overcome this objection. As such, this objection should be withdrawn.

III. Claims 1-4 Define Statutory Subject Matter

At paragraphs 7-9, the Examiner rejected claims 1-4 under 35 U.S.C. §101 for being directed to allegedly non-statutory subject matter. The Examiner suggested that a way to overcome this rejection was to add a “displaying step” to independent claim 1. Although Applicants do not agree that the claims 1-4 only define an algorithm, they have amended the claim 1 to include a displaying step as suggested by the Examiner. Thus, Applicants have overcome the Examiner’s §101 rejection and request that it be withdrawn.

IV. Claims 1-4 are Definite

At paragraphs 10-14, the Examiner has rejected claims 1-4 for being indefinite under 35 U.S.C. § 112, second paragraph. The Examiner has two contentions that allegedly support this rejection. The first is that Steps (b) and (e) of claim 1 recite different types of rankings, and the second is that allegedly the preamble differs from the active steps of claim 1. As will be shown, each of these bases for rejection is traversed.

The Examiner’s first basis for rejection is that the rankings are different at Steps (b) and (e), and clarification is requested. At Step (b), a collection of molecules grown according Step (a) are ranked based on their individual free energy estimates so that the high-ranking molecules with the lowest estimated free energy may be identified. The ranking at Step (e) is based on the actions at Steps (c) and (d). At Step (c), one or more of the functional groups from the high-ranking molecules identified at Step (b) is used as the start fragment for the growth of a set of second-generation molecules. The ranking that is taking place at Step (e) is of these second-generation molecules.

To overcome the Examiner’s first basis for rejection under 35 U.S.C. § 112, second paragraph, claim 1 has been clarified to show the difference in what is ranked at

Steps (b) and (e). Therefore, Applicants request that this basis for rejection for indefiniteness be withdrawn.

The Examiner's second basis for rejecting claims 1-4 for indefiniteness is that the active steps of claim 1 differ from the preamble. Applicants are confused by the Examiner's comments associated with this basis for rejection. The preamble of claim 1 recites that the claim is directed to "de novo" molecular design for a receptor site. This is exactly what takes place at the receptor site according to the active steps of claim 1 and claims 2-4 that depend from claim 1. More specifically, the de novo drug design of claims 1-4 is directed to the development of molecules that are appropriate to bind specific receptor sites. This is accomplished in two phases: (1) Steps (a) and (b); and (2) Steps (c) to (h). There is no incongruity between the preamble and active steps of claims 1-4. Thus, this basis of rejection under § 112, second paragraph is overcome as Applicants understand the rejection. Accordingly, this basis of rejection is overcome and should be withdrawn.

V. Claims 1-4 are Enabling

At numbered paragraphs 15-19, the Examiner has rejected claims 1-4 for being non-enabling. The Examiner's main thrust is that claim 1-4 are enabling for the receptor sites recited in claim 2 but not generally for any receptor site. More specifically, the Examiner is contending that the scope of claims 1-4 should be limited to only the receptor sites recited in claim 2. Applicants submit that this is an undue limitation being suggested by the Examiner.

The specification at page 17, lines 11-14, indicates that in "one embodiment" a receptor site could be selected from the ones set forth in claim 2. Moreover, at page 59, lines 7-10, it states that the receptor sites set forth in claims 2 are preferred, not the only receptor sites for which the present invention is useful. The language that is set forth at these locations of the specification does not indicate in any way that these are the only receptor sites that may be used with the present invention. The receptor sites that are recited at these places in the specification and claimed at claim 2 are to satisfy the best mode requirements of § 112 and not an ultimate limitation for claims 1-4.

If there are receptor sites besides the ones that are recited in claim 2, the process that is set forth in claim 1 still may be used without undue experimentation to build appropriate molecules. The person choosing such a different receptor site would use exactly the same process for the collection and ranking of molecules at Steps (a) and (b), then that person would develop the second-generation molecules according to Steps (c) to (h). Thus, one skilled in the art would know how to make and use the present invention without undue experimentation. Moreover, the Examiner has not indicated anywhere in the specification that would support the contention that claims 1-4 should be limited to only the receptor sites recited in claim 2. Accordingly, Applicants have demonstrated that claims 1-4 should not be limited to only the receptor suites recited in claim 2, but could be used with other receptor sites without undue experimentation and still be within the scope of the present invention.

The Examiner in numbered paragraph 19 contends that protein crystallization is a trial and error method, and unpredictable, and, as such, claims 1-4 are not enabling. Applicants submit that the Examiner may be misunderstanding the present invention.

The section of the specification to which the Examiner points to support that method of the present invention is non-enabling is page 22, line 19 to page 23, line 4. However, the entire section that includes the partial section cited by the Examiner states the following (Page 22, line 16 to Page 23, line 4):

The course-graining model with knowledge-based potential data follows from the application of the principles of canonical statistical mechanics to subsets of proteins. In particular, the model includes the determination that small subsets of a folded protein are in thermal equilibrium with each other. As such, the present invention employs these principles. Thus, there is a reasonable basis to contend that the information present in the crystalline structures of proteins and crystal structures of protein-ligand complexes may be disassembled into constituent parts and the contribution of each part to the binding free energy may be assigned on the basis of probability. This permits the present invention to achieve the more accurate results for binding free energy predictions and applying them in the building of molecules or ligands. [Emphasis added.]

Even in light of the Examiner's statements to the contrary, a person skilled in the art would understand the contributions of the parts of the crystalline structure to binding free energy. The Examiner is to be reminded that according to the present invention these

contributions are to be handled as values that are assigned based on probability. Thus, a person of ordinary skill in the art could carry out these assignments without undue experimentation. The contribution being referred to at this portion of the process is not the principal determination the binding free energy, as the Examiner infers, but, as stated, is to assist in making more accurate predictions which are within the capabilities of a person of ordinary skill in the art without undue experimentation.

Applicants, therefore, have traversed the Examiner's bases for rejection claims 1-4 under 35 U.S.C. § 112, first paragraph, and request that it be withdrawn.

VI. Claims 1-4 are not Anticipated by DeLisi

The Examiner at numbered paragraphs 20-22 rejected claims 1-4 under 35 U.S.C. § 102 for anticipation based on U.S. Patent No. 5,495,423 to DeLisi et al. ("DeLisi"). Applicants submit that pending claims 1-4 are not anticipated by DeLisi.

Claim 1, as amended, recites a method that includes Steps (a) and (b) that are directed to the first selection and ranking of molecules, and Steps (c)-(h) directed to the second-generation molecules that are derived from one or more functional groups of the high-ranking molecules determined at Steps (a) and (b). The DeLisi patent does not disclose or suggest in any way the method of claim 1 that builds a first collection of molecules and then builds second-generation molecules from one or more functional groups of the high-ranking molecules of the first collection. Therefore, DeLisi does not teach or suggest each and every element of claim 1 in the same way as is necessary for DeLisi to anticipate claim 1 of the present application under § 102.

Claims 2-4 depend from claim 1, and, as such, each contain all of the features of claims 1. Since DeLisi does not anticipate claim 1 as demonstrated above, claims 2-4 are not anticipated for the same reasons.

Noting the foregoing, Applicants have traversed the Examiner's anticipation rejection. Thus, Applicants request that this rejection be withdrawn.

VII. Claims 1-4 are not Obvious

At numbered paragraphs 23-28, the Examiner has rejected claims 1-4 under 35 U.S.C. § 103 for obviousness based on U.S. Patent No. 5,495,423 to DeLisi et al. ("DeLisi") in view of *In re Gulack*, 703 F. 2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir.

1983). The Examiner in rejecting claims 1-4 for obviousness contends that “DeLisi et al. discloses the limitations directed toward claim 1...” and *In re Gulack* defines what is nonfunctional descriptive material and when such descriptive material will not distinguish the invention from the prior art in terms of patentability. Applicant submits that the references of this combination taken alone or in combination do not render obvious the invention of claims 1-4 of the present application

As set forth in Section VI above, DeLisi does not teach or suggest the invention of claims 1-4. For these same reasons, DeLisi alone clearly does not render claims 1-4 obvious. The Federal Circuit case *In re Gulack* that the Examiner cited to combine with DeLisi does not in any way overcome the deficiencies in DeLisi to provide a basis for rendering claims 1-4 obvious. Therefore, claims 1-4 are not obvious in light of DeLisi in view of *In re Gulack*, and Applicants request that this obviousness rejection be withdrawn.

The Examiner has also rejected claims 1-4 for obviousness based on DeLisi in view of U.S. Patent No. 6,251,620 B1 to Hatada et al. (“Hatada”). In this combination, DeLisi is cited for disclosing all of the limitations of claim 1 and Hatada is cited for disclosing that three-dimensional structures of SH2 domain proteins have been determined by X-ray crystallography. Applicants submit that claims 1-4 are not rendered obvious by this combination.

As set forth in Section VI above, DeLisi does not teach or suggest the invention of claims 1-4. For these same reasons, DeLisi alone clearly does not render claims 1-4 obvious. Hatada does not in any way overcome the deficiencies in DeLisi to provide a basis for rendering claims 1-4 obvious when it is added to DeLisi. As such, claims 1-4 are not obvious in light of DeLisi in view of Hatada, and Applicants request that this obviousness rejection be withdrawn.

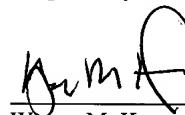
Conclusion

Claims 1-4 are pending in the present application. Applicants have traversed each of the Examiner's bases for objecting to the specification or rejecting the claims, thereby placing the present application in condition for allowance.

The present invention is new, non-obvious and useful. Given that Applicants have traversed each and every objection or rejection raised by the Examiner in the Office Action dated May 12, 2003, the application is in condition for allowance and it is requested that it be passed to issue in due course.

In the event a fee is due, the Commissioner is authorized to charge any required fee to maintain the pendency of this application, or to credit any overpayment to Deposit Account No. 08-0219.

Respectfully submitted,



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